REMARKS

Claims 202-204 are pending. Claim 204 was rejected under 35 U.S.C. §112, first paragraph, and under 35 U.S.C. §112, second paragraph. Claim 202 was rejected under 35 U.S.C. §102(e). Claims 202, 203 and 204 were variously rejected under 35 U.S.C. §103(a).

New claims 205 and 206 have been added herein without prejudice or disclaimer of any previously claimed subject matter.

New claim 205 has been added, reciting a method for suppressing an allergic response to an antigen in a mammal susceptible to an allergic reaction to said antigen. Support for this claim can be found throughout the specification, for example, at page 4, lines 12-14; page 5, lines 13-15; page 6, lines 1-4 and lines 18-21; pages 13-14; page 30, lines 6-9; page 32 lines 22-24; page 33, lines 13-14; page 40, lines 2-8; and Example VII. Administration of the antigen is through administration of the antigen per se or through expression of the antigen from the administered plasmid that encodes the antigen. During the interview on April 25, 2002, the Examiners stated that the specification provided support for both of these embodiments, and that Applicants could claim both embodiments.[1]

New claim 206 has been added, reciting a pharmaceutical composition for stimulating an immune response to an antigen, comprising pREP7 encoding the antigen and a pharmaceutically acceptable carrier. Support for this recitation can be found throughout the specification, for example, at page 4, first full paragraph; page 29, last paragraph; and claim 203.

Therefore, these amendments do not contain any new matter. The Examiner is respectfully requested to enter these amendments.

With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any

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[1] Applicants also draw the Examiners' attention to, for example, claim 4 of U.S. Pat. No. 6,207,646, directed to a method of vaccination which recites that, "a vaccine antigen or an antigen encoded in a DNA vaccine" is administered.

presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Interview

Applicants' representatives wish to thank Examiners Q. Nguyen and D. Nguyen for extending the courtesy of an interview to Applicants' representatives and licensee's representatives and providing helpful suggestions on March 4, 2002 and April 25, 2002. The amendments and remarks reflect discussion and suggestions made during the interviews.

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case in condition for allowance.

Priority

The Office Action states that claims 202-203 are entitled to the priority benefit of the parent application (U.S. Serial No. 08/593,554, filed January 30, 1996) but not the grandparent application (U.S. Serial No. 08/446,691, filed June 7, 1995) or the great-grandparent application (U.S. Serial No. 08/112,440, filed August 26, 1993). Applicants respectfully disagree.

Claim 202 is directed to a composition comprising: a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT, wherein C is unmethylated, and an antigen in a pharmaceutically acceptable carrier, wherein the antigen is encoded in the plasmid. Claim 203 depends from claim 202, further reciting that the plasmid is pREP7 encoding an antigen.

Claims 202 and 203 are entitled to the priority benefit of the great-grandparent application (U.S. Serial No. 08/112,440, filed August 26, 1993). The great-grandparent application describes AACGTT-containing antigen-encoding plasmids that are immunostimulatory. For instance, Example 1 (pages 32-33) of the great-grandparent application discloses the construction of an antigen-expressing vector, pREVk3, based on pREP7. The

pREVk3 vector contains the AACGTT sequence and encodes an antigen, a rearranged kappa light chain. PREVk3 was prepared in *E. coli*, thus the nucleotide C in AACGTT is unmethylated. Example 1 further describes the injection of pREVk3 in a pharmaceutical acceptable carrier, saline (page 33, lines 12-15). Thus, the great-grandparent application, having a filing date of August 26, 1993, discloses compositions exactly as recited in claims 202 and 203.

The Office Action states that there is no support in the great-grandparent application "for the make and use of any plasmid containing an immunostimulatory nucleic sequence comprising AACGTT or 5'CG3' in conjunction or in a combination with an antigen in any form" (original emphasis; page 4 of the Office Action). However, Applicants' preparation and use of the plasmid pREVk3 (Example 1 in the great-grandparent application, see above), which contains AACGTT in combination with the antigen coding sequence, clearly demonstrate the contrary.

Accordingly, Applicants respectfully submit that both claims 202 and 203 are entitled to the benefit of the filing date of August 26, 1993.

Rejections under 35 U.S.C. §112, first paragraph

Claim 204 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

The Examiner states that the specification is enabling for:

- a method of reducing an antigen specific IgE production or for increasing stimulation of an antigen specific TH1 response
- in a mammal comprising
- intradermal injection in said mammal of an effective amount of an immunostimulatory nucleic acid in a plasmid
- said immunostimulatory nucleic acid comprising AACGTT, wherein C is unmethylated, and
- an effective amount of an antigen, wherein said antigen is produced by a process using the plasmid.

The Examiner states that the specification does not reasonably provide enablement for other embodiments of the claims, including: "treating an allergy;" "immunostimulatory nucleic acid comprising 5'CG3';" "administration" and "in a vertebrate." Applicants respectfully traverse this rejection. Each of these elements is addressed in turn below.

Treating an allergy

Claim 204 is directed to a method of treating an allergy comprising administering an effective amount of an immunostimulatory nucleic acid in a plasmid and an effective amount of an antigen (which is encoded in the plasmid) which stimulates production of allergy-associated IgE antibodies.

As noted above, the Examiner states that the specification is "enabling for a method of reducing an antigen specific IgE production or for increasing stimulation of an antigen specific Th1 response." Office Action, page 8. The Examiner also states that "the instant claim encompasses a method for attaining a broad range of therapeutic effects ranging from reducing or alleviating to complete abolishment or preventing symptoms associated with an allergy in a vertebrate (within the scope of treating)" and that there is "no reasonable correlation between the apparent lack of an IgG1 response stimulation and low levels of anti-β-galactosidase IgE levels observed ... with the prevention or abolishment of symptoms associated with any allergy in a vertebrate." Office Action, pages 10-11. (Emphasis added.)

Since antigen-specific IgE is a critical component of allergic reactions and mediates the responses that lead to unpleasant symptoms of allergy, Applicants submit that one skilled in the art would recognize that reduction of antigen-specific IgE antibodies is a desired element in treating allergy. Secreted IgE molecules bind to IgE receptors on the surface of mast cells and basophils. Antigen (allergen) -induced IgE cross-linking on the surface of mast cells and basophils results in release of mediators, such as histamine and leukotrienes, which are responsible for many clinical manifestations of allergic responses. Thus, a reduction in antigen-specific IgE is indicative of a suppression of an allergic response.

In addition to suppressing antigen-specific IgE production, stimulating a Th1 immune response is another aspect of reducing an allergic response in a subject. As taught in the instant specification, "TH1 responses are to be of particular importance in the treatment of allergies and AIDS" and the immunostimulatory nucleic acids of the invention are of "particular use in stimulating the TH1 component in preference to the TH2 component, thus suppressing IgE production in response to the expressed antigen [from the vector]" (page 49, lines 9-10, and page 5, lines 13-15, respectively).

Applicants are not required under 35 U.S.C. § 112, first paragraph, to teach each and every therapeutic effect associated with allergy treatment. Further, in the context of administering an allergen or an allergen encoded by a nucleic acid, one skilled in the art would understand that "treating an allergy" is directed to the goal of suppressing an allergic response, which is also known as allergy immunotherapy or desensitization, and prevention or abolishment of allergy symptoms is not required.

New claim 205 is directed to a method of suppressing an allergic response to an antigen which stimulates production of allergy-associated IgE antibodies comprising administering an effective amount of an immunostimulatory nucleic acid in a plasmid and an effective amount of an antigen (which may be encoded in the plasmid). Applicants respectfully submit that for the reasons discussed above, "suppressing an allergic response" is enabled. During the interview of April 25, 2002, the Examiners indicated that this language would likely be acceptable. Applicants further submit that suppressing an allergic response is not separately patentable with respect to "desensitizing a subject against the occurrence of an allergic reaction in response to contact with a particular allergen" as recited in claim 3 of U.S. Pat. No. 6,207,646.

Thus, Applicants respectfully submit that the specification is enabling for a method of treating an allergy and for a method for suppressing an allergic response.

Immunostimulatory nucleic acid comprising 5'CG3'

The Examiner states that "the specification fails to teach a representative number of immunostimulatory sequences that can induce the same immunostimulatory activity as that mediated by SEQ ID NO:1" and that "the mere possession of the CpG motif in a polynucleotide is not sufficient for inducing the desired immune responses contemplated by Applicants." Office Action, pages 12-13.

Applicants respectfully point out that, in addition to SEQ ID NO:1, the specification lists 18 other "exemplary immunostimulatory polynucleotides of the invention" (pages 13-14) and refers to preferred immunostimulatory nucleic acid sequences such as those described in Krieg et al. ((1995) *Nature* 374:546-549, of record) on page 11. The specification also teaches how to make the immunostimulatory polynucleotides and how to determine whether such an immunostimulatory polynucleotide has the desired effect. See, for example, page 35, line 17, to page 36, line 24 and Examples VII and IX.

Thus, based on the information provided in the specification, one skilled in the art could readily make and test immunostimulatory nucleic acids as used in the claimed methods. Furthermore, the claims require that the immunostimulatory nucleic acids have the recited effect on the immune response. Thus, the claims require that the nucleic acid have immunostimulatory activity as claimed, and exclude those that do not exhibit the claimed activity.

Applicants are not required under 35 U.S.C. § 112, first paragraph, to teach each and every immunostimulatory nucleic acid sequence that will exhibit an effect on an immune response. The specification teaches how to determine whether such an immunostimulatory nucleic acid exhibits an effect on an immune response. Thus, Applicants respectfully submit that the claims are in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph.

Administration

The Examiner states that the specification provides no "support for any other routes of delivering into a vertebrate a plasmid containing an immunostimulatory nucleic acid other than the intradermal injection route that are capable of eliciting the desired selective induction of a Th1 response in a vertebrate upon challenge with an allergen." Office Action, page 15. Applicants disagree this with assertion.

As an initial matter, Applicants respectfully point out that inoperative amounts for any given administration route are not encompassed by this claim due to the claim element of "an effective amount." Claim 204 is directed to a method for treating an allergy that comprises administration of an effective amount of an immunostimulatory nucleic acid in a plasmid and an effective amount of an antigen (encoded by the plasmid) which stimulates production of allergy-associated IgE antibodies to a subject. The route of administration is not an element of the invention as long as effective amounts of the immunostimulatory nucleic acid and an antigen are introduced into the subject.

In concluding that intramuscular administration of "pCMV-lacZ plasmid into a mouse does not induce the desired selective induction of Th1 response" (Office Action, page 15), the Examiner points to the results presented in Figures 13, 15 and 16. Results depicted in these figures are for groups of animals which had received 10 micrograms of plasmid DNA (see figure titles and Examples V and VI). Applicants respectfully point out that these figures indicate low titers for both IgG2a and IgG1 antibodies in this group of mice. In contrast, the results depicted in Figure 17 and described in Example VII, in which IgE levels are suppressed in animals receiving a plasmid containing an immunostimulatory nucleic acid, are based on animals that had received 25 micrograms of plasmid DNA. Thus, these animals received more than twice as much plasmid DNA as the animals whose results are shown in Figures 13-16. Applicants respectfully submit that the apparent lack of a Th1 response in the animals receiving intramuscular administration in Figures 13-16 is just as likely due to the lesser amount of

plasmid administered as due to the route of administration. Accordingly, there is insufficient basis for rejection under 35 U.S.C. §112.

During the March 4, 2002 interview (and reiterated in the interview on April 25, 2002), the Examiners suggested that the claim be directed to "parenteral administration" of the immunostimulatory nucleic acid and Applicants have introduced this limitation into new claim 205. The specification describes that compositions for administration in the methods of the invention may be mixed with pharmaceutically acceptable carriers, including parenteral and intravenous vehicles. See, for example, page 30, lines 6-9. In addition to intradermal administration, a number of other parenteral administration routes are described in the specification such as subcutaneous, transdermal, intranasal, topical, vaginal and intramuscular. See, for example, page 33, line 14, page 40, lines 3-8, and Example VI. As discussed in the interview of March 4, 2002, Applicants submit that parenteral administration is not separately patentable in view of administration as is recited in claim 3 of U.S. Pat. No. 6,207,646.

Applicants respectfully submit that rejection of claim 204 based on the alleged lack of enablement for the scope of route of administration is improper, since the rejection would equally apply to claim 3 of U.S. Pat. No. 6,207,646 in which no particular route of administration is specified. Thus, in order to make this rejection, the rejection must have the approval of the Technology Center Director. M.P.E.P. § 2307.2, § 1003.

In a vertebrate

The Examiner states that the specification is not enabled for a method of treating an allergy in a vertebrate and states that "it is unclear whether the desired selective induction of TH1 response that is beneficial for treating an allergy could be obtained in numerous species encompassed within the broad genus of a vertebrate." Office Action, page 16.

The specification describes methods for stimulating a Th1 immune response and/or suppressing a Th2 immune response in a host such that an allergy is treated. Thus, to the extent

that a Th1 response is stimulated and/or a Th2 response is suppressed in a given vertebrate, the claimed methods are in compliance with the enablement requirement.

Nevertheless, in the interest of expediting prosecution, Applicants have added claim 205 directed to a method for suppressing an allergic response in a mammal. Applicants submit that suppressing an allergic response to an antigen in a mammal through stimulating a Th1 response and/or suppressing a Th2 response is well known in the art.

Applicants note that claim 3 of U.S. Pat. No. 6,207,646 is directed to a method for desensitizing a subject against the occurrence of an allergic reaction in response to contact with a particular allergen. The specification of U.S. Patent No. 6,207,646 describes a subject as "a human or vertebrate animal including a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, mouse, etc." Column 13, lines 27-29. All but one of these 11 examples of non-human vertebrate animals are mammals. Applicants submit that in the area of allergy treatment, treating a mammal is not separately patentable in view of treating a subject as is recited in claim 3 of U.S. Pat. No. 6,207,646. During the interview of March 4, 2002, the Examiners indicated that these are not separately patentable inventions.

Applicants respectfully submit that rejection of claim 204 based on the alleged lack of enablement due to administration to a vertebrate is improper, since the rejection would equally apply to claim 3 of U.S. Pat. No. 6,207,646 wherein administration is to a subject which includes "a vertebrate animal". Thus, in order to make this rejection, the rejection must have the approval of the Technology Center Director. M.P.E.P. § 2307.2, § 1003.

In sum, Applicants submit that the rejection of claim 204 has been adequately addressed in view of the above remarks and that the pending claims are in compliance with the enablement requirement. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

Claim 204 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicants respectfully traverse this rejection.

The Examiner states that "an effective amount of an antigen (a protein or a peptide) is not a part or portion of a plasmid (a nucleic acid molecule) being administered." Office Action, page 18. However, as recited in claim 204, an effective amount of an antigen is administered through the administration of a plasmid encoding the antigen, "wherein said antigen is encoded in the plasmid." Thus, Applicants submit it is clear that for this to occur the antigen is expressed from the plasmid in the host receiving the plasmid.

Claim 205 recites that either antigen or antigen encoded in the plasmid is administered.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. §102(e)

The rejection of claim 202 under 35 U.S.C. §102(e) as allegedly being anticipated by Davis (U.S. Pat. No. 5,780,448) as evidenced by Krieg et al. (U.S. Pat. No. 6,194,388, "Krieg") is respectfully traversed for the reasons set forth below.

As discussed above, claim 202 is entitled to the benefit of the great-grandparent application (U.S. Serial No. 08/112,440), filed August 26, 1993. According to the Office Action, Davis and Krieg have effective filing dates of November 7, 1995 and July 15, 1994, respectively. Therefore, neither Davis nor Krieg is prior art with respect to claim 202 under 35 U.S.C. §102(e).

In addition, Applicants wish to point out that even if claims 202 and 203 are deemed properly rejected, new claim 206 is not subject to the same rejection. Claim 206 is directed to a pharmaceutical composition for stimulating an immune response to an antigen, comprising pREP7 encoding the antigen and a pharmaceutically acceptable carrier. The great-grandparent

application discloses, throughout the application, that naked nucleotides encoding an antigen can be used to stimulate an immune response. Examples of such disclosure can be found at page 12, lines 4-7 and page 13, lines 19-22. The great-grandparent application also discloses that these naked nucleotides can be combined with a pharmaceutically acceptable carrier, for example, in claim 14 and at page 24, lines 15-23. The great-grandparent application further discloses that pREP7 is a plasmid vector that can be used to express the antigen, for example, at page 23, lines 17-18 and in Example 1. Therefore, claim 206 is fully supported by the great-grandparent application, which was filed on August 26, 1993. Thus, Krieg and Davis do not constitute prior art with respect to claim 206.

Accordingly, this rejection is improper and Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. §103

Claims 202 and 203

Claims 202 and 203 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Krieg et al. (U.S. Pat. No. 6,194,388, "Krieg") in view of Davis (U.S. Pat. No. 5,780,448). Claims 202 and 203 further stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Krieg in view of Applicants' admission (Amendment C filed October 31, 2001 in paper No. 28, page 8, second last paragraph and page 9, second paragraph). Both of these rejections are respectfully traversed for the reasons articulated below.

Both claims 202 and 203 are entitled to the priority benefit of the great-grandparent application (U.S. Serial No. 08/112,440), which was filed on August 26, 1993. As stated in the Office Action, the effective filing date of Krieg is July 15, 1994, and that of Davis is November 7, 1995. Since both of these references are dated later than the priority date of claims 202 and 203, neither is prior art with respect to the rejected claims. Therefore, claims 202 and 203 are not rendered unpatentable by the combination of Krieg and any other references.

As Applicants noted above in the discussion of the 35 U.S.C. §102(e) rejection, even if claims 202 and 203 are deemed properly rejected, new claim 206 is not subject to the same rejections.

Accordingly, withdrawal of these rejections is respectfully requested.

Claim 204

Claim 204 stands rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Terr (Allergy desensitization, pages 739-743, 1992) in view of Krieg et al. (U.S. Pat. No. 6,194,388, "Krieg") and Davis (U.S. Pat. No. 5,780,448). Claim 204 stands rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Terr in view of Krieg and Applicants' admission of record (Amendment C filed 10/31/01 in Paper No. 28, page 8, second last paragraph and page 9, second paragraph).

Applicants respectfully submit that rejection of this claim based on 35 U.S.C. §103 in view of the cited references is improper since the rejection would equally apply to claim 3 of U.S. Pat. No. 6,207,646. U.S. Pat. No. 6,194,388 is prior art under § 102(e) to U.S. Pat. No. 6,207,646 since these patents have different inventive entities. Thus, in order to make this rejection, the rejection must have the approval of the Technology Center Director. M.P.E.P. §§ 2307.2, 1003.

Nevertheless, Applicants respectfully traverse this rejection and submit that the cited references do not support a *prima facie* case of obviousness, and, as such, this rejection is properly withdrawn.

To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the cited reference (or references when combined) must teach or suggest all the claim limitations. These requirements are summarized in the M.P.E.P. (M.P.E.P. §2143, and §2143.01 to §2143.03), and

are based on well-settled case law: *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). If any of these three criteria are not met, a *prima facie* case of obviousness has not been established.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established because (a) there is no motivation to combine the cited references; and (b) even if the references were combined, there is no reasonable expectation of success, based on the teachings of the references.

Terr describes two adjuvants proposed to be of use in allergy immunotherapy based on the particular antigen delivery properties of each, and there is no teaching in any of the cited references that immunostimulatory nucleic acids have these properties. Thus, there is insufficient basis for extrapolating and applying the teachings of Terr to immunostimulatory nucleic acids. As outlined below, Terr further indicates that in the context of allergy immunotherapy, each of these adjuvants is associated with negative results. Thus, the cited references provide no basis for one of skill in the art to substitute immunostimulatory nucleic acids for the adjuvants described in Terr. Further, use of immunostimulatory nucleic acids with an allergen in an allergy treatment arises from the understanding that immunostimulatory nucleic acids can induce or stimulate a Th1 immune response and can shift a Th2 immune response toward a Th1 immune response. None of the cited references describe that immunostimulatory nucleic acids can generate a Th1 response or can shift a Th2 response toward a Th1 response.

No motivation to combine Terr with Krieg or Davis

There is no motivation to combine Terr with Krieg or Davis. Terr describes only two adjuvants, incomplete Freund's adjuvant and alum, that have been administered with allergen in allergy desensitization therapies. There is no teaching or suggestion in Terr that an immunostimulatory nucleic acid is a suitable adjuvant for allergy immunotherapy, and the Examiner acknowledges this lack of teaching ("Terr does not teach the use of any

immunostimulatory nucleic acid comprising 5'CG3' in a plasmid as an adjuvant"; Office Action, page 25). Other than incomplete Freund's adjuvant and alum, Terr does not teach or suggest the use of any adjuvant for use with an allergen.

Further, the two adjuvants described by Terr, incomplete Freund's adjuvant and alum, provide no basis for one skilled in the art to believe that an immunostimulatory nucleic acid would be suitable for use in allergy immunotherapy. Terr teaches that incomplete Freund's adjuvant "enhances the immune response by providing an insoluble lipid depot in the subcutaneous tissue from which droplets of allergen are gradually released, thereby stimulating repeated injections of allergen over time" and that this treatment "was probably similar in effectiveness to conventional multi-injection desensitization." Page 743, col. 1.[2]

According to Terr, incomplete Freund's adjuvant was effective as an allergen adjuvant because it provided a "depot" of allergen so that gradual release of allergen mimicked multiple injections of allergen. In contrast, none of the cited references provides any teaching that when combined with an antigen, immunostimulatory nucleic acids provide an insoluble depot of the antigen that allows for gradual release of the antigen after administration.

Terr also states that adsorption of "allergens onto alum produces an insoluble antigen that is more efficiently phagocytosed by macrophages." Page 743, col. 1-2.[3] There is no teaching or suggestion from Krieg or Davis regarding macrophage uptake of immunostimulatory nucleic acids. Thus there is no teaching or suggestion in the references that this mechanistic basis for using alum would likewise apply to immunostimulatory nucleic acids.

The teachings of Krieg and Davis provide no motivation to combine either of these references with Terr. Krieg teaches that immunostimulatory oligonucleotides can be

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[2] As discussed below, Terr further teaches that using this adjuvant was a failure: "This form of therapy was abandoned because of concern about potential carcinogenicity." Page 743, col. 1.

[3] As discussed below, Terr goes on to state that "hoped-for advantages over aqueous allergens - fewer injections and improved efficacy - have not been achieved" Page 743, col. 2.

"administered to a subject in conjunction with a vaccine, as an adjuvant, to boost a subject's immune system to effect better response from the vaccine". Column 17, line 65, to column 18, line 1. Davis teaches that copies of "CpG motifs in DNA expression vectors act as adjuvants facilitating the induction of an immune response against an expressed protein." Column 7, lines 18-21.[4] There is no teaching or even suggestion that this immune stimulation is appropriate for the allergy context.

Neither Krieg nor Davis describe or suggest that immunostimulatory polynucleotides comprising 5'CG3' can be used in treating an allergy or to reduce an allergic response to an antigen. Given this lack of teaching in Krieg and Davis about suitability or applicability of using immunostimulatory nucleic acids in the allergy context, their teaching of using immunostimulatory nucleic acids to induce an immune response (Krieg; Davis) and in a vaccine (Davis) clearly only applies to conventional vaccines, not in allergy immunotherapy.

Further, neither Krieg nor Davis describe that the immunostimulatory polynucleotides can generate a Th1 response or can shift a Th2 response to a Th1 response. This was the critical observation needed in order to understand that these immunostimulatory nucleic acids could be suitable for allergy therapy. *See* specification at page 49, lines 9-10 ("TH1 responses are to be of particular importance in the treatment of allergies and AIDS."). The second-issued Krieg patent, U.S. Pat. No. 6,207,646, which does contain reference to using immunostimulatory nucleic acids for allergy therapy[5] (in contrast to the cited Krieg patent, which contains no such disclosure), connects applicability of immunostimulatory nucleic acids to the allergy context based on the observation regarding stimulation of a TH1 response: "Based on the ability of the immunostimulatory nucleic acid molecules to shift the immune response in a subject from a Th2

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[4] In contrast to the Examiner's statement, Krieg does not disclose using immunostimulatory nucleic acids in conjunction with an "antigen". Krieg only refers to vaccines.

[5] In U.S. Pat. No. 6,207,646, the disclosure regarding the use of immunostimulatory nucleic acids for allergy therapy is entitled to the October 30, 1996 filing date of U.S. Application No. 08/738,652, which is later than Applicants' January 30, 1996 priority date.

(which is associated with production of IgE antibodies and allergy) to a Th1 response (which is protective against allergic reactions), an effective dose of an immunostimulatory nucleic acid (or a vector containing a nucleic acid) alone or in conjunction with an allergen can be administered to a subject to treat or prevent an allergy." Column 34, lines 18-26. There is no such teaching in any of the cited references relating to stimulation of the Th1 response and applicability to allergy.

Thus, Applicants submit that there is no motivation in these references, or in the art, to combine the teachings of Terr with Krieg and Davis, or the teachings of Terr with Krieg and Applicants' admission, to arrive at the present invention. As such, this rejection may be properly withdrawn.

No reasonable expectation of success

Applicants also respectfully submit that, although there is no motivation to combine these references, even if the references were combined, one skilled in the art would have no reasonable expectation of success of the claimed invention from the teachings of Terr with the secondary references.

First, there is no teaching in any of the cited references that the mechanisms of action posited for each adjuvant disclosed by Terr are shared by immunostimulatory nucleic acids, and as such, there is no reasonable expectation of success based on the teachings about incomplete Freund's adjuvant and alum.

According to Terr, incomplete Freund's adjuvant was effective as an allergen adjuvant because it provided a "depot" of allergen so that gradual release of allergen mimicked multiple injections of allergen. In contrast, the references provide no teaching that when combined with an antigen, immunostimulatory polynucleotides provide an insoluble depot of the antigen that allows for gradual release of the antigen after administration. Thus, from the cited references, one skilled in the art would have no expectation that substitution of immunostimulatory polynucleotides for incomplete Freund's adjuvant in an allergen therapy regimen would be effective in suppressing an allergic response.

Terr also teaches that allergens adsorbed onto alum are more efficiently phagocytosed by macrophages. Page 743, cols. 1 and 2. In contrast, the cited secondary references (Krieg and Davis) provide no teaching that when combined with an antigen, immunostimulatory nucleic acids are more efficiently phagocytosed by macrophages. Thus, there is no basis in the cited references for an expectation that substitution of immunostimulatory polynucleotides for alum in an allergen therapy regimen would be effective in suppressing an allergic response.

Second, Terr teaches that there were significant drawbacks or shortcomings with respect to each of the adjuvants disclosed. With respect to incomplete Freund's adjuvant, Terr stated that this form of therapy "was abandoned because of concern about potential carcinogenicity." Page 743, col. 1. With respect to alum, Terr states that that "hoped-for advantages over aqueous allergens - fewer injections and improved efficacy - have not been achieved." Page 743, col. 2. Such negative results do not create a reasonable expectation of success with respect to using another adjuvant, and there is no basis given this teaching for an expectation that immunostimulatory nucleic acids would be suitable in the allergy immunotherapy context.

From Terr's teaching of the lack of success of the combination of alum and allergen in allergy therapy and the secondary references' silence with regard to the use of immunostimulatory polynucleotides in the treatment of allergy, one skilled in the art would have no expectation of success of the claimed invention.

Thus, the combination of Terr with the secondary references provides no expectation of success of the claimed invention for one skilled in the art. On this basis, the rejection may be properly withdrawn.

In sum, Applicants submit a *prima facie* case of obviousness has not been established and accordingly, respectfully request withdrawal of the rejection of claim 204 under 35 U.S.C. §103.

U.S. Patent No. 5,804,566

During the interview of April 25, 2002, the Examiners brought to Applicants' attention U.S. Patent No. 5,804,566 (Carson et al., filed November 1, 1994, "the '566 patent"), suggesting that this patent may be potentially relevant to the patentability of claims 204-205. Applicants have the following comments regarding the '566 patent and U.S. Patent No. 6, 194,388 ("Krieg").

Claims 204-205 are directed to methods of treating allergy or suppressing an allergic response by administering an immunostimulatory nucleic acid comprising 5'CG3' and an antigen (antigen per se or encoded antigen) which stimulates production of allergy-associated IgE antibodies. The '566 patent teaches, *inter alia*, methods of treating allergies induced by an antigen by administration of naked polynucleotides which operatively encode the antigen. Other than the requirement that the polynucleotides encode the allergy-inducing antigen, no particular nucleotide sequences of the polynucleotides are taught as required in the methods of the '566 patent.

Krieg does not describe or suggest that the immunostimulatory polynucleotides can generate a Th1 response or can be used in treating allergy. Rather, Krieg teaches oligonucleotides containing unmethylated 5'CG3' dinucleotides that can be used to stimulate immune responses, including antigen-specific B cell activation and NK cell stimulation. Nowhere does Krieg teach or suggest that the 5'CG3' containing oligonucleotides can be used to suppress, rather than stimulate, an immune response, let alone an allergic response.

Reiteration of request for interference

Applicants respectfully reiterate their request that the Office institute interference proceedings between this application and U.S. Pat. Nos. 6,194,388 and 6,207,646, as set forth in the Request for Interference under 37 C.F.R. § 1.607, provided herewith. Applicants note that an interference may be declared if one of Applicants' claims is allowable. 37 C.F.R. § 1.606; M.P.E.P. § 2306. Thus, even if the Examiner believes one or more of the claims are not

patentable, declaration of an interference should not be deterred as long as at least one of the claims is allowable.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, he is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 02-4800**, referencing docket no. 028723-306. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: May 9, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

202. A composition comprising:

a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT, wherein C is unmethylated, and an antigen in a pharmaceutically acceptable carrier, wherein the antigen is encoded in the plasmid.

203. The composition of claim 202, wherein the plasmid is pREP7 encoding an antigen.

204. A method of treating an allergy in a vertebrate, comprising administering to the vertebrate an effective amount of an immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising 5'CG3', wherein C is unmethylated, and an effective amount of an antigen which stimulates production of allergy-associated IgE antibodies in the vertebrate, wherein said antigen is encoded in the plasmid.

205. (New) A method for suppressing an allergic response to an antigen in a mammal susceptible to an allergic reaction to said antigen which stimulates production of allergy-associated IgE antibodies in the mammal, comprising parenterally administering to the mammal

(a) an effective amount of an immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising 5'CG3', wherein C is unmethylated, and

(b) an effective amount of the antigen or the antigen encoded in the plasmid.

206. (New) A pharmaceutical composition for stimulating an immune response to an antigen, comprising pREP7 encoding the antigen and a pharmaceutically acceptable carrier.